

# A Case Series of Scrub Meningoencephalitis from a Tertiary Care Center in North India

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## Abstract

Scrub typhus infection is reemerging leading cause of acute febrile illnesses in post-rainy or monsoon season in Southeast Asia. It is caused by *Orientia tsutsugamushi* and spread by the bite of chiggers, larval forms of trombiculid mites. The clinical picture can range from simple acute febrile illness to multiorgan dysfunction. Neurological manifestations also vary from aseptic meningitis, meningoencephalitis, cerebral infarction, acute disseminated encephalomyelitis, transverse myelitis, and psychiatric manifestations. Here, we present a case series of eight cases of scrub meningoencephalitis diagnosed based on clinical, laboratory, and radiological criteria.

**Keywords:** CSF (cerebrospinal fluid), ELISA (enzyme-linked immunosorbent assay), RT-PCR (reverse transcriptase–polymerase chain reaction), scrub typhus

## INTRODUCTION

Scrub typhus is a common, zoonotic disease in Southeast Asia caused by *Orientia tsutsugamushi* and over the years due to rapid urbanization; it has become a major public health problem in India.<sup>[1]</sup> Clinical features of scrub typhus infection can range from nonspecific symptoms such as fever with myalgia to acute liver injury, acute renal damage, acute respiratory distress, myocarditis, or central nervous system involvement. Scrub typhus infection can have various neurological complications such as meningoencephalitis, meningitis, cerebral infarction, cerebellitis, cranial nerve palsies, plexopathy, transverse myelitis, neuroleptic malignant syndrome, and Guillain–Barré syndrome.<sup>[2,3]</sup>

## MATERIAL AND METHODS

Eight cases of scrub meningoencephalitis aged >18 years were diagnosed among cases of acute encephalopathy syndromes admitted from March 2017 to May 2018 (n = 105) at the Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India. The diagnosis of scrub meningoencephalitis was based on the presence of the following features and laboratory investigations: fever + headache ± altered sensorium ± neck signs + cerebrospinal fluid (CSF) cytology (predominantly lymphocytes) with moderate elevation of protein and low-to-normal glucose with or without polymerase chain reaction (PCR)-CSF positivity + positive serum immunoglobulin M (IgM) serology-positive and/or blood/eschar PCR (+). Data were recorded pro forma for demographic details, laboratory investigations, and outcomes. Other central nervous system (CNS) infections were ruled out in all eight cases with negative CSF tuberculosis (TB)-PCR, herpes

simplex virus (HSV)-PCR, enterovirus-PCR, and Japanese encephalitis (JE) IgM serology.

## RESULTS

Females outnumbered males by 5:3 with a mean age of  $30.75 \pm 7.22$  years. Predominant symptoms other than fever and altered sensorium were vomiting in four (50%), headache in three (37.5%), and seizures in two patients (25%). Other symptoms included myalgia (n = 1) and shortness of breath (n = 2). The mean Glasgow coma scale was  $8.25 \pm 1.83$  of 15 on presentation. The mean systolic blood pressure was  $104 \pm 20.05$  mm of Hg, and the mean diastolic blood pressure was  $60 \pm 11.87$  mm of Hg. The mean pulse rate was  $100.5 \pm 21.42$  per minute, and the respiratory rate was  $22.5 \pm 5.4$  per minute. Two patients had systolic pressure <80 mm of Hg. The mean duration of presentation of symptoms was  $8.375 \pm 1.76$  days with a duration of stay of  $7.85 \pm 4.6$  days.

Seven patients had serum IgM positivity, and four were PCR-positive for scrub typhus. CSF analysis showed raised

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**Table 1: Demographic, clinical, and laboratory profile of patients with scrub encephalitis**

Parameter	Value
Male:Female	3:5
Mean age (yrs)	30.75±7.22
Mean duration of symptoms (days)	8.375±1.76
Fever	8/8 (100%)
Altered sensorium	8/8 (100%)
Headache	3/8 (37.5%)
Vomiting	4/8 (50%)
Seizures	2/8 (25%)
Systolic blood pressure (mm of Hg)	104±20.05
Diastolic blood pressure (mm of Hg)	60±11.87
Pulse rate (per min)	100.5±21.4
Respiratory rate (per min)	22.5±5.4
Hemoglobin (gm per dL)	11.2±1.8
Total leukocyte count (per mm <sup>3</sup> )	10625±4550.27
Platelet count (per mm <sup>3</sup> )	206.75X 10 <sup>3</sup> ±80.8X10 <sup>3</sup>
Total bilirubin (mg per dL)	0.9±0.81
Blood urea (mg per dL)	39.37±15.01
Serum creatinine (mg per dL)	0.8±0.3
Mean Glasgow coma scale	8.25±1.83
Scrub IgM positivity	7/8
Scrub PCR positivity	4/8
Coinfection (malaria, dengue, enteric and leptospirosis)	None
Cerebrospinal fluid analysis	
Total cells (per mm <sup>3</sup> )	122.5±105.5
Neutrophilic/lymphocytic predominant	4/3
Protein (mg per dL)	177.63±179.3
Sugar (mg per dL)	82±90.7
Scrub PCR	0/8
Abnormal MRI	2/8
Mean duration of stay (days)	7.85±4.6
Outcome (mortality)	2/8

protein and normal sugar in most cases with predominant neutrophils in four cases and lymphocytosis in three cases. The mean CSF cells were  $122.5 \pm 105.5$  per mm<sup>3</sup> and protein of  $177.63 \pm 179.3$  mg per dL [Table 1]. Cerebrospinal fluid analysis for scrub typhus PCR was negative in all patients. The most common abnormality seen on the magnetic resonance imaging (MRI) brain was leptomeningeal enhancement; there was no other specific abnormality noted in patients on MRI. Two of the eight patients expired. Five patients required mechanical ventilation. Of the eight patients, two patients expired with raised intracranial pressure being the possible cause of death [Table 2]. All patients received an empirical antibiotic injection of ceftriaxone 2 gm intravenous twice a day, and six patients received an injection of acyclovir 10 mg per kg per dose thrice a day as per the hospital guidelines for the acute encephalitic syndrome. Six patients received an injection of doxycycline 100 mg twice a day followed by oral therapy after receiving a serological diagnosis of scrub typhus. After this study, there was a change in the antibiotic policy of the institute with the addition of doxycycline or azithromycin for

acute encephalitic syndrome in view of the increased number of cases related to scrub typhus infection.

## DISCUSSION

Scrub typhus is a zoonotic infection caused by *Orientia tsutsugamushi*. Typhus is derived from typho, which means fever with stupor in Greek. It is predominantly present in a geographical area known as the tsutsugamushi triangle. India is situated at the western end of this triangle. Over the past decades, it has emerged and reemerged in various countries in South-east Asia. Neurological involvement in rickettsial infection is recognized ever since the origin of typhus infection. CNS complications, especially meningoencephalitis, usually occur in the second week of the disease.<sup>[4]</sup> The common clinical spectrum of neurological involvement in scrub typhus infection cases includes aseptic meningitis, meningoencephalitis, isolated cranial nerve palsies, acute disseminated encephalomyelitis, opsoclonus, transverse myelitis or longitudinally extensive transverse myelitis, stroke, Guillain-Barré syndrome, and psychiatric features. Although our patient cohort had a female predominance of 5:3, various studies have shown male preponderance. The mean age was around  $30.75 \pm 7.22$  years, which also concurs with other studies. Our patients had encephalitic features with the presence of seizures in two cases and opsoclonus in one case. The mean Glasgow coma scale score was  $8.25 \pm 1.83$  of 15. The mean duration of symptoms was  $8.375 \pm 1.76$  days suggestive of presentation in 2<sup>nd</sup> week of illness, which is the usual presentation time of neurological features of scrub typhus infection.<sup>[4]</sup> Usual features of patients with a meningitis form of scrub typhus infection present with headache, vomiting, and neck stiffness. Neck stiffness may be reported in up to 67% of patients. Seizures and altered sensorium are predominant in encephalitic forms.<sup>[5]</sup> Neurological presentation of scrub typhus infections occurs due to small-vessel vasculitis, leading to the secondary breakdown of the blood-brain barrier and culminating in cerebral microinfarctions and edema.<sup>[6]</sup> Direct invasion of the brain by the organism is known, and it has been seen to grow in the cerebrospinal fluid.<sup>[7]</sup> Rickettsial deoxyribonucleic acid (DNA) has been isolated in cerebrospinal fluid using the nested PCR technique.<sup>[8]</sup> Focal exudates of mononuclear cells in the leptomeninges and hemorrhage in the brain parenchyma seen in the autopsy specimens of fatal scrub typhus cases also reveal the neurotropic nature of this organism.<sup>[9]</sup> Mahima Mittal *et al.*<sup>[10]</sup> during the 2015 outbreak in Gorakhpur, India, showed that scrub was the etiological agent in more than 60% of acute encephalitis syndrome (AES) cases. Scrub typhus was also found to be the most common etiological agent of AES around 25% of total positive cases (180/540), in a study conducted in Bihar, India.<sup>[11]</sup>

Cerebrospinal fluid analysis usually does not show any particular patterns such as other acute encephalitic syndromes. There is a mild-to-moderate elevation of CSF protein (usually more than 50 mg%) along with lymphocytic pleocytosis with low-to-normal CSF glucose. Similar findings were seen in our

**Table 2: Demographic, clinical, and laboratory details of all eight cases of scrub meningoencephalitis**

Parameters	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Age (years)	24	35	25	27	45	35	30	25
Sex	Female	Male	Male	Female	Female	Female	Female	Male
Duration of symptoms (days)	7	10	7	10	10	6	10	7
Fever	+	+	+	+	+	+	+	+
Altered sensorium	+	+	+	+	+	+	+	+
Headache	+	-	+	-	-	+	-	-
Seizures	+	-	-	-	-	-	-	+
Vomiting	+	-	+	-	-	+	-	+
GCS (Glasgow coma scale)	7	8	7	10	5	10	10	9
Hemoglobin (g/dL)	9.4	13.2	12.3	12.4	10.3	10.4	8.5	12.9
Total leukocyte count (/ $\mu$ l)	5600	18400	10400	13400	11900	11300	10400	3600
Platelet count ( $\times 10^3/\mu$ l)	179	290	293	236	279	99	182	96
Sodium/potassium (mEq/L)	145/3.7	139/4.4	130/2.9	121/2.5	147/3.0	141/4.8	134/3.9	145/3.5
Blood urea/serum creatinine (mg/dl)	32/0.7	47/0.7	27/0.6	27/0.6	49/0.8	33/0.6	70/0.8	30/1.5
Total bilirubin (mg/dL)	1.4	0.2	0.3	0.2	0.4	0.7	2.3	1.8
CSF analysis								
Total cells	0	20	80	140	200	40	200	300
Differential count (%)	N0/L0	N70/L30	N100/L0	N80/L20	N40/L60	N0/L100	N10/L90	N80/L20
Protein (mg/dL)	298	80	563	8	169	119	144	40
Sugar (mg/dL)	59	62	40	305	65	40	48	37
Scrub CSF-PCR	-	-	-	-	-	-	-	-
Scrub typhus IgM	+	+	+	+	+	+	+	-
Scrub PCR in blood	-	-	+	+	+	-	-	+
MRI brain findings	Diffuse leptomeningeal enhancement	Normal	NA	Mild hydrocephalus	NA	NA	Diffuse meningeal enhancement	Normal
Mechanical ventilation	Yes	Yes	No	Yes	Yes	Yes	No	No
Outcome	Discharged	Discharged	Discharged	Died	Died	Discharged	Discharged	Discharged

N = Neutrophils, L = Lymphocytes, CSF = Cerebrospinal fluid analysis

study. The raised CSF protein level has no relation to the rise in cells so an albumino-cytological dissociation is observed.

Serological assays either by enzyme-linked immunosorbent assay (ELISA) or indirect immunofluorescence assay have the mainstay for the diagnosis of scrub typhus. With the development of specific PCRs, the diagnosis of scrub typhus has improved. 56-kD protein sequencing of genes by PCR from human blood samples is found to be useful in the early diagnosis of scrub typhus. Refinements such as nested PCR assays with the sequencing of genotype-specific genes encoding 56-kD protein help in further differentiating various genotypes of *Orientalis tsutsugamushi*.<sup>[8]</sup> The study by Parul Jain *et al.*<sup>[11]</sup> also showed that though CSF reverse transcriptase (RT-PCR) can be used to diagnose scrub meningoencephalitis, the yield is low as only seven of 419 CSF samples were positive by RT-PCR, whereas 74 samples patients had a positive IgM scrub typhus by ELISA in serum.

There are no definite or diagnostic radiological findings in scrub meningoencephalitis. The CT scan was normal in seven of 8 cases with the presence of hypodensities in the temporal, orbitofrontal, and hypothalamus region in one case. MRI brain findings in our series included leptomeningeal enhancement

in two cases of five patients. Chin Jo Chua *et al.* from Kuala Lumpur reported a 40-year-old patient with scrub typhus diagnosed serologically based on high IgM titer and increasing IgG titer, whose MRI brain showed small ring enhancing lesions in the corpus callosum and hyperintensities on fluid-attenuated inversion recovery (FLAIR) and T2-weighted sequences in periventricular and deep white matter regions of the brain.<sup>[12]</sup> Ayan Kar *et al.*<sup>[11]</sup> observed that in all the five patients who were positive for scrub typhus by serological method and had encephalopathy, the neuroimaging showed features of diffuse cerebral edema with the involvement of putamen and thymus in T2-weighted images and FLAIR hyperintensities of the same, implying primary involvement of the brain tissue. In one of the studies by UK Misra *et al.*,<sup>[13]</sup> MRI was done in 25 patients of 31 patients with scrub typhus meningoencephalitis, and all the MRIs were normal except in one case of meningeal enhancement. In our study, two patients expired of eight cases of scrub encephalitis (25% fatality). The case fatality rate was around 16.6% in a study from a highly endemic area in India.<sup>[14]</sup> High clinical suspicion should be kept for scrub encephalopathy or encephalitis as it can have overlapping features with other acute encephalitic syndromes such as HSV, dengue, and Japanese encephalitis and usually

occurs in monsoon or post-monsoon season. Timely diagnosis with clinical clues such as eschar and rapid diagnostic tests with early initiation of therapy with doxycycline can lead to better outcomes. Neurological recovery is usually good in these patients with fewer long-term sequelae as compared to HSV or JE.<sup>[13]</sup>

## CONCLUSION

Scrub meningoencephalitis is an emerging cause of acute encephalopathy syndrome in India, especially in the post-rainy season. There are no definite CSF or MRI abnormalities to differentiate it from other acute encephalitis syndromes. High clinical suspicion should be kept while managing such cases in endemic areas in post-monsoon season.

## Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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